

Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1. (currently amended) An antibody that binds specifically to an autophosphorylated form of Inositol Requiring 1 (IRE1), and does not substantially bind to an unphosphorylated form of IRE1.
2. (original) The antibody of claim 1, wherein the antibody is a monoclonal antibody.
3. (original) The antibody of claim 1, wherein the antibody is an antigen-binding fragment of a monoclonal antibody.
4. (original) The antibody of claim 3 wherein the fragment comprises an Fab, F(ab')₂, Fv or single chain Fv.
5. (original) The antibody of claim 1, wherein the antibody is a polyclonal antibody.
6. (original) The antibody of claim 5, wherein the polyclonal antibody is PIRE1A1.
7. (currently amended) A method of determining an endoplasmic reticulum (ER) stress level in a cell or biological sample, the method comprising detecting an Inositol Requiring 1 (IRE1) activity level in the cell or biological sample by detecting the level of autophosphorylated IRE1, wherein an increase in the IRE1 activity level indicates an increase in ER stress, and a decrease in the IRE1 activity level indicates a decrease in ER stress.
- 8-12. (cancel)

13. (original) The method of claim 7, wherein an IRE1 activity level is detected by detecting the ratio of autophosphorylated to unphosphorylated IRE1.

14. (currently amended) The method of claim 13, wherein the level of ~~phosphorylated~~ autophosphorylated IRE1 is detected using an antibody that binds specifically to an autophosphorylated form of IRE1.

15. (currently amended) The method of ~~any one of claims 7-14~~ claim 7, wherein the ER stress level is determined in a cell.

16. (currently amended) The method of ~~any one of claims 7-14~~ claim 7, wherein the ER stress level is determined in a mammalian cell.

17. (currently amended) The method of ~~any one of claims 7-14~~ claim 7, wherein the ER stress level is determined in a human cell.

18. (currently amended) The method of ~~any one of claims 15-17~~ claim 15, wherein the cell is a pancreatic beta cell or a peripheral lymphocyte.

19. (currently amended) The method of ~~any one of claims 7-18~~ claim 7, wherein the ER stress level is determined in a cell extract.

20. (currently amended) A method of diagnosing an ER stress disorder in a subject, the method comprising determining a level of ER stress in a sample comprising a cell isolated from the subject[[,]] using a method according to ~~any one of the preceding claims 7-19~~ claim 7, wherein an increased level of ER stress is indicative of an ER stress disorder in the subject.

21. (currently amended) A method of monitoring the progression of an ER stress disorder in a subject, the method comprising determining a level of ER stress in two or more samples comprising a peripheral blood cell isolated from the subject at sequential time points[[,]] using a method according to ~~any one of claims 7-19~~ claim 7, wherein a change in level of ER stress indicates the progress of the ER stress disorder.

22. (currently amended) The method of claim 20 [[or 21]], wherein the ER stress disorder is diabetes.

23. (currently amended) The method of ~~any one of claims 20-22~~ claim 20, wherein the cell is a peripheral blood cell.

24. (currently amended) A method of identifying a test compound that modulates endoplasmic reticulum (ER) stress, the method comprising:

providing an ER stress model system;
optionally, increasing ER stress in the system;
contacting the system with a test compound; and
evaluating ~~one or more of:~~

—————(i) a level of Inositol Requiring 1 (IRE1) activity in the system by measuring a level of autophosphorylated IRE1 in the presence and absence of the test compound, ~~and/or~~

—————(ii) ~~a level of HMG CoA Reductase Degradation (HRD1) activity in the system in the presence and absence of the test compound,~~

wherein an increase in the level of IRE1 activity, ~~and/or an increase in the level of HRD1 activity~~ indicates that the test compound causes an increase in ER stress, and a decrease in the level of IRE1 activity indicates that the test compound causes a decrease in ER stress.

25. (original) The method of claim 24, wherein the ER stress model system is a cell or animal model of an ER stress disorder.

26. (original) The method of claim 24, wherein ER stress in the system is increased by contacting the system with an agent that increases levels of ER stress.

27. (original) The method of claim 26, wherein the agent that increases ER stress is thapsigargin or tunicamycin.

28. – 29. (cancel)

30. (currently amended) The method of claim [[29]] 24, wherein the level of IRE1 autophosphorylation is measured using an antibody that binds specifically to the autophosphorylated form of IRE1.

31. (original) A kit for determining ER stress, the kit comprising:
~~one or more primers for amplifying a region of X Box Binding Protein 1 (XBP 1)~~
~~mRNA that includes a splice site, or portion thereof;~~
~~one or more of: a control comprising a spliced XBP 1 nucleic acid and a control~~
~~comprising an unspliced XBP 1 nucleic acid; and~~
the antibody of claim 1 and instructions for use.

32. (original) The method of claim 24, further comprising:
contacting an ER stress model system with a candidate compound that increases IRE1 and/or HRD1 activity; and
evaluating ER stress in the system in the presence of the candidate compound,
wherein a decrease in ER stress in the system in the presence of the candidate compound indicates that the candidate compound is a candidate therapeutic agent for the treatment of an ER stress disorder.

33. (original) The method of claim 24, further comprising:
providing a model of an ER stress disorder;
optionally, increasing levels of ER stress in the model;
contacting the model with a candidate therapeutic agent for the treatment of an ER stress disorder identified by the method of claim 33; and
evaluating the levels of ER stress in the system in the presence of the candidate compound,
wherein an improvement in the model in the presence of the candidate therapeutic agent indicates that the agent is a therapeutic agent for the treatment of an ER stress disorder.

34. (currently amended) The method of ~~any of claims 24-33~~ claim 24, wherein the compound or agent is a nucleic acid, polypeptide, peptide, or small molecule.

35. -46. (cancelled)

47. (new) The method of claim 21, wherein the ER stress disorder is diabetes.

48. (new) The method of claim 21, wherein the cell is a peripheral blood cell.